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PELLAGRA AND ITS POSSIBLE RELATION TO MAIZE ACCORDING TO SOME RECENT VIEWS.—A REVIEW.

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Raubitschek [1] seems to have been the first to take up, in an experimental way, the question as to the effects of exposure to sunlight upon maize-fed animals in association with the question of a possible relation to the etiology of pellagra. His first communication was apparently of a more or less preliminary character, and quite recently he has published a much more important paper upon the subject.[2]

It is the purpose of the present article to review briefly this paper as well as the papers of two other authors on the same subject, and to add a few details on certain matters germane to the views expressed.

In his last paper, above mentioned, Raubitschek, in his introduction notes the immense mass of literature which has accumulated on the etiology of pellagra, and speaks in the harshest terms of the very questionable kind of work which has been done in this field.

He also comments on the fact that only seldom have the somewhat scanty results of pathologico-anatomical results been employed in attempts to clear up its etiology; and that modern microbiologic, especially serologic technic has never, to any extent, been so used. The work which has been done, he adds, is composed in great part of misinterpreted researches on the feeding of animals, incomplete metabolic investigations, and the piling up of statistical details.

After very briefly mentioning some of the literature, he places the theories of the etiology of pellagra in three groups: The *Bacterial*, the *Toxic*, and the *Autotoxic*. These theories are then briefly reviewed in a general way, and he concludes that not one of them, in its present state, can be considered satisfactory.[3]

Finally he observes that if the real cause of pellagra is unknown, we must not insist too closely upon bringing the disease into strict causal relation with the use of maize as food; and that if any real progress is to be made, the above theories must be tested in a satisfactory experimental way, especially upon pellagrins, before they can be accepted as of real importance.

[1] Wiener klinische Wochenschrift, vol. 23, No. 26, June, 1910.
[2] Centrlblt. f. Bakt., 1 Abt. Originale, Bd. 57, Heft. 3.
[3] It is to be noted that neither here nor elsewhere in his paper has the author taken any cognizance whatever of the more recent ideas of a protozoal or similar origin of pellagra.

He then takes up his own experimental work in several sections, as follows:

BACTERIOLOGIC INVESTIGATIONS.

He found it possible to study only briefly the numerous microorganisms which have been isolated from both good and spoiled maize [1] by various workers, and presented as the cause of pellagra. The numerous molds, which can be especially grown from spoiled corn, met the same fate. Since raw corn is not directly consumed as food, but only products prepared from it, he deemed the bacteriologic investigation of prepared (cooked) food worthy of more consideration than the raw material.

Nevertheless in a preliminary investigation, largely as a matter of orientation, he did take up in a general way the flora of raw maize and compared his results with the literature. He thought certain isolated cultures which exhibited a tolerance to high temperatures were of especial importance in consideration of the cooking of food.

The various bacteria and molds were too numerous for detailed study, so he soon confined himself to work on food prepared from maize, especially since he found that relatively few of the microorganisms withstood a temperature of 100° C. Such microorganisms suggested a line of work looking to the establishment of an infection of the gastro-intestinal tract by food prepared from corn.

With this end in view he prepared polenta and cakes from both good and bad corn. These preparations were opened under sterile precautions, and from the inside cultures were made on suitable media, and grown mostly under aerobic conditions. In a few cases he recovered some species of *Penicillium* and *Aspergillus*, but chiefly the *Bacterium Maydis*. Usually his cultures were sterile.

Next he turned to the bacteriologic investigation of pellagrins themselves, and in this work he kept especially in mind the ideas of Ceni on aspergillary infections as a cause of pellagra.

Blood cultures from an arm vein were made from pellagrins in all stages of the malady (media and details not given), and his results were constantly and invariably negative.

Bacteriologic investigation of the stools of pellagrins (again details not given) convinced him that the intestinal flora of pellagrous persons differed in no essential way from that of healthy individuals. At first there appeared to be an unusual occurrence of the *B. Maydis* in pellagrous stools, but further work showed this bacterium to be, in summer, just as frequent in the stools of healthy persons, possibly as the result of the consumption of such raw foods as salads, etc.

Finally bacteriologic investigation of the organs of pellagrins a few hours after death gave essentially negative results (details not given).

He concluded therefore that there exists no basis for a parasitic etiology of pellagra.

[1] Throughout this article maize, corn, and Indian corn are used interchangeably; likewise the terms bad, spoiled, and damaged, as applied to corn, are used synonomously to express a definite and decided deterioration of the grain under the influence of parasitic growths thereon; by good corn is meant grain which has not undergone this change.

SEROLOGIC-BIOLOGIC INVESTIGATIONS.

Under the idea that pellagra is due to an almost exclusive maize diet he thought the possible appearance of specific antibodies in the blood serum of pellagrins a matter of much importance.

Accordingly he prepared maize extracts (details given), and tried, with proper technic, to obtain a "precipitin" reaction in blood sera collected from numerous pellagrins in all stages of the disease. The results were always positive. In his control work, however, with both healthy persons and animals, he obtained the same result. Hence he concluded that this reaction possesses neither diagnostic nor biologic value. He omitted detailed protocols as useless and unnecessary.[1]

In a similar manner he also made use of the complement-fixation reaction, and here again nothing characteristic could be observed. His controls displayed the same result seen with the sera of pellagrins, viz, absence of hemolysis.[2]

Next he tried experiments for hypersusceptibility in pellagrins and in healthy persons by means of the ophthalmo and cutaneo-reactions with various maize extracts. All of these results were negative.[3]

These experiments, he says, still leave for proof how pellagrins, fed for a short time on a good mixed diet, would react to a suddenly administered maize diet.

It also remains to be shown whether pellagrins, on a long-continued maize diet, may be sensitized from the intestinal tract, and whether they would react from a new supply of maize albumen with important symptoms of hypersensitization, such as vertigo, fever, vomiting, and diarrhea, all of which is important if pellagra have any causal relation with a maize diet.

Still it is evident that both sound persons and pellagrins bear a short exclusive maize diet without reactions.

Further experiments were made upon the phenomena of anaphylaxis in animals to determine the presence of maize antibodies. Pellagrins in all stages of the disease were bled from a vein of the arm, and these sera in various quantities (5 to 10 c. c.) were injected intraperitoneally into guinea pigs. Twenty-four hours later intravenous injections of the same sera (up to 3 c. c.) were made into these pigs. These animals showed reactions not observably different from the controls injected with sera from normal persons.

He concludes from the work of this section that antibodies specific for maize albumens (from good or bad maize) do not occur in the serum of pellagrins. If these negative results do not permit any definite conclusion, still it would appear that from them one may infer that any causal relation between maize diet (good or bad) and pellagra is pure speculation.

TOXINE INVESTIGATIONS.

In these experiments he sought to determine whether maize, naturally or artificially spoiled, would produce deleterious effects upon animals if used in rational doses.

[1] In a footnote he states that Italian authors have described this reaction as characteristic of pellagra, but apparently without controlling their work (Riv. Pel. ital., 1909).
[2] He does not state in these experiments whether his controls were upon a diet of maize.
[3] Compare Hirschfelder, Archives Internal Med., vol. 6, No. 5, p. 614, for similar results.

For this purpose he made use of good corn and spoiled corn obtained from pellagrous regions, ground under proper precautions, and extracted for 24 hours in sterile tap water. He also made extracts from a maize porridge or broth which had been inoculated with various pure cultures isolated either from bad maize or pellagrous stools.

The extracts he obtained were variously colored and some possessed a fatty-acid like odor. They were kept a long while in the ice chest under toluol without apparently undergoing further change.

With these extracts he injected rabbits (subcutaneously, intraperitoneally, and intravenously) and mice and guinea pigs (subcutaneously and intraperitoneally). In one series he used large doses, up to 8 c. c.; in another series daily small subcutaneous doses for one to two weeks; in another series various extracts were daily mixed with the food of the animals.

In no case were changes observed which by any means could be brought to show any causal relation between pellagra and a maize diet. Frequently the animals refused the food, and hence lost weight, but in no way did the experiments justify any idea whatever that corn contains a toxic substance which by long use may lead to pellagroid phenomena in animals.

He concluded that the negative results of these experiments are worthy of note, since it would appear from them that not one of the above-mentioned theories is supported by these results, and not one seems to bear comparison with actual facts.

* * * * * * *

The author here begins another part of his paper with a preliminary discussion. He points out that the pellagrous erythema is usually confined to the exposed surfaces of the body, and thinks that from this it may be inferred either that there is a reduced resistance of the entire body surface and hence exposed parts are unduly sensitive to slight noxious influences (sunlight), or that eventually, under the influence of a maize diet, in the body surfaces exposed to sunlight, there is developed a noxious substance (Noxe), which produces not only local morbid changes but also affects the entire organism. This thought is further justified by the usual occurrence of pellagrous skin changes at that season when the field laborer is most exposed to the sun. It is possible, then, that there may be some relation between a maize diet, sunlight, and pellagra. He also refers to the work of Aschoff [1] in support of this view.

He directs attention to the analogy with buckwheat poisoning (fagopyrismus) in animals. In this condition white or spotted animals, exposed to the light, suffer, while the dark animals or white animals kept in the dark, escape. In this condition general as well as local symptoms are noticed.

The active body in the buckwheat is soluble in organic solvents, and seems to be a fat or lipoid, in the wide sense, and is possibly related to the vegetable lipochromes.

All these phenomena stand in near relation to the so-called photodynamy, viz, that under the influence of certain fluorescent color stuffs, the effect of light on exposed body surfaces, in animals, is to

[1] Ueber die Wirkungen des Sonnenlichtes auf den Menschen. Vortrag gehalten in der Naturforschenden Gesellschaft zu Freiburg i. Br. am 5 Marz 1908, Freiburg und Leipzig, 1908; und die Lichtstrahlen als Krankheitsursache (Handb. d. allg. Pathol., herausg. von L. Krehl u. F. Marchand. Bd. I, p. 159) Leipzig.

produce erythema and other skin changes with eventual death of the animal. It would seem, then, that some such idea may be entertained for a similar relation of things in pellagra, for in corn there occurs a fluorescent color stuff, and in bad corn is also found a characteristic red material (Lombroso). This idea opens up a new field for investigation. The author refers to Hausmann's work.[1]

FEEDING EXPERIMENTS WITH MAIZE UNDER THE INFLUENCE OF SUNLIGHT.

These experiments are shown in the tables which follow. These tables do not appear in the author's paper, but are made up from the data given by him in order that his results may be more easily understood.

Certain preliminary explanations are necessary, and these apply to all of the tables unless otherwise stated. The animals used were white and gray mice. They were kept in large, airy, clean cages, under constant weight control, and each individual mouse was marked for identification. In each cage there were placed 25 white and 5 gray mice. Some cages were exposed daily to direct sunlight, some were protected from light by heavy, dark paper; some were kept in almost absolute darkness. The general symptoms displayed by the sick animals were: Great loss in weight, paretic weakness, especially of the hind legs, sometimes apathy, sometimes increased nervous irritability; later emaciation, hyperæmia of noses and ears, sometimes falling of the fur, and finally in many cases cramplike seizures. The foods given were mixed diet composed of wheat bread, cooked turnips, cheese scraps, etc.; good polenta composed of good meal boiled in salt solution; bad polenta composed of spoiled maize prepared in the same way; rice composed of broken rice also cooked in the same way. In some cases the author leaves his results stated in an indefinite way, and this is indicated in the tables by a ?, which means that the statement is not definite, but the inference is justifiable. The + sign in the column marked "Sunlight" means exposure to sunlight; the − sign means kept in a condition of darkness, as described. The + sign in the column marked "Symptoms" means the appearance in the animals of the symptoms described above; the − sign means the animals remained well.

I. SERIES TO TEST EFFECT OF MAIZE DIET AND EXPOSURE TO SUNLIGHT.

[Time, summer.]

Cage.	Sunlight.	Food.	Symptoms (4 weeks and 6 to 8 weeks).	Remarks.
A	+	Mixed	White (−), gray (−)	All (−) animals gained weight. Pathological and bacteriological investigations made in all (+) animals, with negative results.
B	+	Good polenta	White (+), gray (−)	
C	+	Rice	White (+), gray (−)	
a	−	Mixed	White (−), gray (−)	All animals gained in weight.
b	−	Good polenta	White (−), gray (−)	
c	−	Rice	White (−), gray (−)	

[1] Not to work on pellagra, but to several papers on photodynamic substances and their effects. See Wien. Klin. Wchnschr., 1908, No. 44, and 1909, No. 52; also Biochem. zeitschr., Bd. 14, p. 275, and Bd. 15, p. 12.

II. SERIES TO TEST EFFECTS OF QUALITY OF MAIZE.

[Time, summer.]

Cage.	Sunlight.	Food.	Symptoms (4 weeks and 6 to 8 weeks).	Remarks.
A	+	Good polenta	White (+), gray (−)	Animals fed on bad polenta did not relish the food, and hence lost weight. Cage B only some gray mice survived to the end of the experiment.
B	+	Bad polenta	White (+), gray (−)	
C	+	Rice	White (+), gray (−)	
a	−	Good polenta	White (−), gray (−)	Cage b, all animals survived to the end. Cage c, all died of an intercurrent malady which time did not permit to investigate.
b	−	Bad polenta	White (−), gray (−)	
c	−	Rice	White (−), gray (−)	

III SERIES. EFFECTS OF INCREASED INTENSITY OF LIGHT.

[Time, February, March, April, and May. Increased intensity of sunlight began to be apparent in early April. No symptoms previously.]

Cages.	Sunlight.	Food.	Symptoms, February and March.	Symptoms, April.	Remarks.
A.	+	Mixed	All (−)	All (−)	Cage B last of May and first of June, all 5 white died. Cage C same time, all 10 white died. Earlier one gray died from unknown cause. Cage D, same time, all white died?
B.	+	Good polenta	All (−)	All (+) except gray?	
C.	+	Bad polenta	All (−)	All (+) except gray	
D.	+	Rice	All (−)	All (+) except gray	
a.	−	Mixed	All (−)	All (−)?	
b.	−	Good polenta	All (−)	All (−)?	
c.	−	Bad polenta	All (−)	All (−)?	
d.	−	Rice	All (−)	All (−)?	

III SERIES, SECOND PART. TO TEST CHANGE OF DIET AFTER APPEARANCE OF SYMPTOMS.

First days of May transferred.	Symptoms last of May and first of June.	Remarks.
10 white from B to A	All slowly died	Rest in same cage remained well.
10 white from B to b	2 died	All others remained well and gained weight, but not so much as those which had been in cages from the beginning.
15 white from C to c	1 died	

In commenting on the second part of Series III, the author thinks it evident that a simple change in diet perhaps hinders the lethal result of maize feeding under exposure to light, but can not prevent it.

He concludes from these experiments that a diet of maize (good or bad), when administered under the influence of sunlight, is deleterious to white mice, and that in this we have relations closely analogous to what is seen in fagopyrismus. The effect of rice diet he reserves for later comment.

MAIZE COLOR STUFFS AND MAIZE OIL.

He next undertook certain chemical investigations of maize, with especial reference to color stuffs similar to the lipochromes and soluble in organic solvents. He also paid attention to the fats found in this grain and notes that all previous observers have laid stress on fat-containing cereals.

By a series of chemical procedures, which he gives in more or less detail, he finally obtained the following substances: From good maize, a reddish yellow oily fluid and a waxy yellowish material; from spoiled maize two similar substances but of a more grayish color and possessing a foul odor. Wider researches were not undertaken as unnecessary for his purposes.

This maize oil and this waxy (fatty) substance were used in further experiments given below. For use by injection the substances were taken up in olive oil and heated to body temperature.

Subcutaneous injections in this way were administered to white and black rabbits, colored guinea pigs, and mice under different conditions of light and darkness. The results were of little value beyond showing that these substances were poorly absorbed and locally very irritating.

The following table, compiled as were the previous tables, shows his results with fat-free maize and maize fat. The maize fat seems to be the waxy material already referred to above. By fat-free maize is meant the maize left after extraction with organic solvents, usually hot alcohol.

I SERIES. FEEDING FAT-FREE MAIZE.

Cage.	Sunlight.	Food.	Symptoms (8 weeks).	Symptoms (10 weeks).
A	+	Good polenta	All died except gray	
B	+	Good fat-free maize	Slight loss weight	
C	+	Bad fat-free maize	do	
a	−	Good polenta	Slight loss weight	
b	−	Good fat-free maize	do	
c	−	Bad fat-free maize	do	

II SERIES. FEEDING MAIZE FAT.

A	+	Good polenta	All died (except gray?)	
B	+	Good fat-free maize	All (−)?	All (−)?
C	+	Maize fat		All died (except gray?).
a	−	Good polenta	All (−)?	All (−)?
b	−	Good fat-free maize	do	Do.
c	−	Maize fat		Only slight loss weight.

From these experiments he concluded that by alcoholic extraction of maize meal (removal of fat) the active body is removed, and hence for this reason extracted polenta, free of fat and color stuffs, even under the influence of sunlight, is not directly harmful as a food. He deemed Series II very important in its results.

GENERAL CONCLUSIONS AND REMARKS.

He assembles here the conclusions already stated in the body of the paper. He thinks he has demonstrated the presence of a photodynamic stuff in maize, and that this material is soluble in alcohol. He brings out strongly the effect upon the animals of changing the conditions of light without any modification of diet, and discusses briefly the symptoms displayed by the animals.

He declares that he does not attempt to bring his experimental results into a strict relation with the etiology of pellagra, or to assume

for this disease a photodynamic basis, or even to conclude that pellagra is produced by an almost exclusive diet of maize, good or bad, which displays its harmful effects first under the influence of light. The inference is apparently that his results are very suggestive but not as yet conclusive.

He comments on certain feeding experiments of other workers and points out that the conditions of light under which their animals were kept may explain some of their irregular results.

He notes the effect of rice diet in his animals, and says this cereal also is rich in fat, and by many is held accountable for a disease somewhat analogous to pellagra, viz, beriberi.

Finally he makes brief reference to the work of two other investigators.

A review of the papers of these two authors shows that they have reported experimental work on this phase of pellagra. Their work seems to have been done independently of each other and of Raubitschek, and all at about the same time.

Lode's[1] work seems not to have been published in full, but at a medical meeting at Innsbruck he demonstrated a number of guinea pigs which he had fed on corn and kept exposed to sunlight.

He stated that in his experiments he had found that guinea pigs, on a maize diet, exposed to sunlight, suffered after eight days from falling of the hair. This phenomenon increased up to the seventeenth day. Guinea pigs kept in the dark, on the same diet, displayed no changes. All of the animals lost weight.

In his experiments he made use of a yellow variety of maize, and he suggests an analogy to what is observed in fagopyrismus.

Animals fed upon white maize or alcohol-extracted maize, under sunlight, were negative up to the eighteenth day. They did not lose weight.

His results furnished occasion for suggesting the use of white varieties of maize in the prophylaxis of pellagra.

Horbaczewski,[2] in a long paper, reports similar experimental work with very similar results. He discusses at some length the possibilities involved, and makes suggestions very similar to those of Raubitschek and Lode.

In his experimental work he largely made use of mice, and his results in a general way agree with those obtained by Raubitschek. He made use of a very much smaller number of animals, and the details need hardly be repeated here. He also worked with a color stuff and with fatty materials which he prepared from maize.

The symptoms displayed in his animals were very similar to those of Raubitschek, but the vaso-motor phenomena were much more marked, and autopsies showed frequent inflammatory conditions in the gastro-enteric tract with fatty changes in the abdominal viscera.

In discussing his final conclusions he says that the possibility should be borne in mind that pellagra and pellagroid affections may be due not only to the use of maize as a food, but also to the use of other grains or other plant stuffs which are eaten in various localities. Hence observations at various places and at various times might help to explain the vexed question of a "pellagra without maize."

[1] Wien Klin. Wochenschr., No. 31 (Sitzung der wissenschaftl. Aertzgesellsch. in Innsbruck vom 30 Juni 1910).

[2] Oesterr. Sanitätswesen. Beilage zu No. 31 vom 4 August, 1910.

COMMENTS.

This phase of the etiology of pellagra is comparatively new and has as yet attracted little attention in English literature. Raubitschek's first paper is briefly noticed in American literature,[1] and Sambon has also commented upon it.[2] Apparently he does not regard it of great importance and states that it in no way explains the epidemiological relations of pellagra.

The question of *photodynamic substances* and their effects is a large one, with a rather extensive literature. References have been already given to some of this.[3] It may be briefly said in a general way that a great number of fluorescent bodies, both vegetable and animal, which are harmless in the dark, have been shown to possess highly toxic properties in the light, especially direct sunlight. These properties include the power of exerting a deleterious influence on animal body cells and on certain protozoa. In this series of substances are found certain normal constituents of the animal body, such as hematoporphyrin.

Fagopyrismus is an interesting condition which arises in white or white-spotted animals, fed on buckwheat and exposed to the sunlight. It does not develop in dark animals nor in white animals kept away from the light. It is due not only to buckwheat but to other species of *polygonum*, and may arise from the eating not only of the green plant, and especially at the time of flowering, but also of the grains, straw, stubble, and chaff. It occurs especially in lambs and swine, more rarely in cattle, and very rarely in horses. The symptoms will return even three or four weeks after discontinuance of the food if the animal be exposed to strong sunlight. In winter the eruption is restricted to a mere itching and burning.

The symptoms consist of a severe erythema of the skin, or even a severe dermatitis, and there may be an associated disturbance of respiration, with general symptoms referable to the central nervous system, more particularly if the skin around the head be involved. There seems to be some question as to whether the condition is caused by certain irritant products exerting only a local action on the skin, with secondary general manifestations, or whether it is due to some toxic substance produced in the body of the animal under the influence of sunlight.[4]

Experimental work on laboratory animals, however, seems to show clearly that there is developed some toxic substance in the body of the animal. Öhmke[5] fed rabbits, mice, and guinea pigs on buckwheat and death resulted in the white animals exposed to diffused sunlight. The symptoms were loss of hair, paralytic phenomena, and disturbances of respiration. White animals kept in the dark and the gray animals showed no changes.

The chaff as well as the grains gave the same results. Alcoholic extracts of the buckwheat showed a noticeable fluorescence, and proved just as harmful as the buckwheat, while the buckwheat left after extraction was harmless.

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[1] Pellagra, Marie, trans. by Lavinder and Babcock, Columbia, S. C., 1910.
[2] Journal Trop. Med. and Hyg. 1910, XIII, 23, 363.
[3] An important work on this subject is Die sensibilisierende Wirkung fluorescierender Substanzen by Tappeiner and Jodlbauer, Leipzig, 1907.
[4] Friedberger and Frohner, Veterinary Pathol., trans. by Hayes, 1908, vol. 1, p. 458.
[5] Zentralblatt für Physiologie, 1909, XXII, 22, 685.

Buckwheat poisoning in man seems to have been very rarely noted. Smith [1] reports a case, but the condition in this patient seems to have been different from what is seen in animals. The man exhibited a high degree of hypersusceptibility to buckwheat and displayed the phenomena usual to anaphylaxis. But the question of exposure to light did not come into consideration. It may be said that we really know very little of buckwheat poisoning in man, as the condition seems very rare.

The relation between the pellagrous erythema and exposure to sunlight has always attracted attention among those interested in this disease, and there seems to be no doubt that some such relation does exist. This relation is, however, not always a very definite one. Pellagrous erythemas are not usual, but at the same time are not uncommon, on covered parts of the body; and Neusser long ago observed that in the gypsy children of Roumania, who go about naked, the pellagrous erythema is usually confined to local situations, hands, feet, and face. It is worthy of note also that the dark-skinned races suffer from pellagra and from its erythema, and that the negro of the Southern States exhibits erythemas just as extensive and just as severe as those seen in the whites.

If the coloring matters of corn are of such importance as is implied above, then it is likely that the varieties of corn may be a matter of importance. The Italians, in their prophylactic measures, have come to regard the yellow varieties as less likely to undergo spoiling, and they condemn the use of white varieties. White varieties of corn are rarely seen in Italy. Raubitschek does not state what varieties he used in his work, but they were likely yellow. Lode makes the point clear and Horbeczewski states in several places that he used *cinquantino*, which is a yellow corn.

With regard to beriberi and rice, it is interesting to note that Fraser and Stanton [2] in their experimental work of feeding fowls with rice, state that alcohol-extracted rice produced the same phenomena as the rice before such extraction; and that rice, which had been proved harmless, after being extracted with alcohol, produced typical phenomena in fowls, but that if a quantity of the extract, freed of alcohol, were given at the same time the birds remained well.

Finally it is to be remarked that the results of feeding experiments upon animals are very difficult of interpretation, and conclusions can be drawn therefrom only with the utmost caution. Hunt [3] says in reporting some recent work of this character:

* * * Although there is a vast accumulation of the most accurate knowledge of foods from the dynamic and economic points of view, little is known of the specific action of the various foods.

Feeding experiments with maize, made by workers interested in pellagra, have produced many discordant results, and very varied interpretations. To apply results of this kind to the explanation of a specific disease of man is difficult and uncertain. Such application must be made from wide knowledge, broad experience, and good judgment.

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[1] Archives of Int. Medicine, 1909, Vol. III, p. 350.
[2] Philip. Jour. Science, 1910, B. Med. Sc., Vol. V, No. 1.
[3] Bulletin No. 69, Hygienic Laboratory, United States Public Health and Marine-Hospital Service, Washington.